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10/536,563	09/26/2005	Jouji Kokuzawa	082386-000100US	7075
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EXAMINER				
SAJJADI, FEREDOUN GHOTB				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/536,563

Applicant(s)

KOKUZAWA ET AL.

Examiner

FEREYDOUN G. SAJJADI

Art Unit

1633

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 September 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 4-8 and 15-18 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 4-8 and 15-18 is/are rejected.
- 7) ☒ Claim(s) 18 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SI/08)
- 4) ☐ Interview Summary (PTO-413)
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____
- Paper No(s)/Mail Date _____

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicants' amendment dated September 17, 2008, in response to the non-final action dated March 21, 2008, has been entered. Claim 4-6 and 18 have been amended, and claims 19-23 cancelled. No claims were newly added. Accordingly, claims 4-8 and 15-18 are pending in the application and under current examination. The claims have been examined commensurate in scope with the elected species of the invention.

New Claim Objections

Claim 18 is newly objected to because of the following informalities: in line 2, the words "wherein the" have been duplicated. Appropriate correction is required.

Response to Claim Rejections - 35 USC § 112- New Matter

Claims 6 and 18-21 were previously rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement, and introducing new matter into the disclosure of an application, in the office action dated March 21, 2008. Applicants' cancellation of claims 19-21 obviates their rejection. Applicants have amended claim 18 to direct the majority of differentiated cells to neurons. Accordingly, the rejection is hereby withdrawn. Applicants' arguments are moot in view of the withdrawn rejection.

New Claim Rejections - 35 USC § 112- New Matter

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 4-6 are newly rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art (hereafter the Artisan), that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR §1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Claims 4-6 have been amended to recite: "a growth medium supplemented with a combination of growth factors consisting of hepatocyte growth factor (HGF) and fibroblast growth factor-2 (FGF-2)". Applicants state that support is found, for example on page 13, lines 23-25; on page 15, lines 10-11; and on page 29, line 23 through page 30, line 1. However, the instant specification appears devoid of support for the limitation of a growth medium supplemented with a combination of growth factors consisting of HGF and FGF-2.

Page 13 of the specification describes the addition of HGF to a culture medium containing FGF-2, EGF, or a combination thereof; page 15 describes growth medium supplemented with HGF; and pages 29-30 describe growth medium containing FGF-2 and/or EGF, supplemented with various concentrations of HGF. The specification therefore utilizes open language with reference to the addition of HGF and FGF-2. However, the instant specification is silent on growth medium that is limited in its supplementation to only HGF and FGF-2. Thus, at the time the application was filed, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of culturing, proliferating and differentiating neural stem cells in growth medium "consisting of HGF and FGF-2", as instantly claimed.

MPEP 2163.06 notes: "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire

application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure". This is a new matter rejection.

Response & Maintained Claim Rejections - 35 USC § 102

Claims 4-6, 8 and 15-18 stand rejected under 35 U.S.C. 102(c) as being anticipated by Csete et al. (U.S. Patent No.: 6,589,728; filed Jan. 31, 2001). The rejections set forth on pp. 3-4 of the office action dated August 3, 2007, and pp. 4-7 of the previous office action dated March 21, 2008 are maintained for reasons of record.

As indicated in the previous office actions, Csete et al. teach a method for isolating, maintaining, enriching and differentiating stem or precursor central nervous system cells from fetal rat brain, that are dissociated to a single-cell suspension and plated on tissue culture dishes in medium containing bFGF. Further teaching that the medium for isolation, proliferation and differentiation of the stem cells may be supplemented with a variety of growth factors, cytokines and serum, that include hepatocytes growth factor (HGF) (column 7). Csete et al. teach that the medium for proliferating the stem cells and the medium for differentiation of these cells can be the same or different (lines 42-45; column 7). Csete et al. further teach that the isolated progenitor cells may optionally be manipulated to express desired gene products, by transfection prior to expansion and differentiation (column 12), which constitutes the genetic modification of the cells. Thus teaching all the limitations of instant claims; FGF-2 and bFGF being synonymous terms for the same growth factor.

Applicants traverse the rejection, arguing that the claimed methods require culturing or differentiating a neural stem cell in cell culture to a growth medium supplemented with a combination of growth factors consisting of hepatocyte growth factor (HGF) and fibroblast growth factor-2 (FGF-2), and the claims have been amended to set forth language that excludes supplementing the growth medium with growth factors other than HGF and FGF-2. Further arguing that Csete does not expressly, implicitly or inherently disclose or suggest culturing, proliferating or differentiating a neural stem cell by supplementing a growth medium with a

combination of growth factors consisting of HGF) and FGF-2. Applicants' arguments have been fully considered but are not found persuasive.

In response, it is noted that the claims 4-6 as amended recite "a growth medium supplemented with a combination of growth factors consisting of hepatocyte growth factor (HGF) and fibroblast growth factor (FGF-2)". However, the claims do not recite a growth medium consisting of HGF and FGF-2. As a growth medium may comprise serum (or any of a number of growth factors) for example, the presence of other growth factors in the growth medium cannot be excluded. It is merely the supplementation of the growth medium that has been limited to HGF and FGF-2.

Applicants argue that the Examiner appears to be basing this rejection on the passage located at column 7, lines 42-62 in Csete, referring generally to undefined stem cells/progenitor cells, but does not call out neural stem cells in particular, disclosing that the [culture] medium can be supplemented with a variety of growth factors, cytokines, serum, etc. and proceeds to list at least 11 different growth factors, at least 4 different hormones, and at least 3 different cytokines. But Applicant's invention is a selection invention that requires culturing, proliferating or differentiating a neural stem cell in particular by supplementing a growth medium with a combination of growth factors consisting of HGF and FGF-2 in particular.

Such is not found persuasive, because contrary to Applicants' assertion, the rejection is based on the teachings of Csete et al. as a whole, and not the just the selected passage in column 7. Methods for isolating, culturing, and differentiating neural stem or progenitor cells in medium containing bFGF (a.k.a. FGF-2) are described in column 15, lines 40-65). In column 7, Csete et al. state: "It is understood that the initial medium for isolating stem/progenitors, the medium for proliferation of these cells, and the medium for differentiation of these cells can be the same or different." (lines 42-45). Further teaching that the medium for isolation, proliferation and differentiation of the stem cells may be supplemented with a variety of growth factors, that include hepatocytes growth factor (HGF). Thus Applicants cannot ignore the teachings of Csete et al. as a whole and base their conclusions on selective parts of the teachings of the prior art reference.

Applicants argue that Csete also refers to U.S. Patent No. 5,750,376 ("Hazel and Muller"), which discloses proliferating neuroepithelial cells in medium supplemented with bFGF. Hazel and Muller disclose that in order to induce differentiation to neurons and glia, the medium containing bFGF is removed and replaced with medium lacking bFGF; and that nowhere in Csete is it disclosed or suggested to supplement a medium with hepatocyte growth factor to culture, proliferate or differentiate neural stem cells preferentially into neurons.

Such is not found persuasive. As an initial matter, it is noted that as evident from the claimed invention, including the teachings of Applicants' specification and the methods of claims 4 and 5, the very same growth medium supplemented with HGF and FGF-2 is used for the culturing and proliferation, as that for differentiation. The reference in Csete et al., to the method of Hazel and Muller represents one embodiment of their invention. Further, instant claim 6 is the only claim directed to the differentiation of neural stem cells, but does not provide any specific condition with regard to the composition of the medium, that is separate from the condition for culturing and proliferating. Csete et al. disclose a method for isolating, maintaining, enriching and differentiating stem or precursor cells from fetal rat brain, comprising culturing in medium containing hepatocytes growth factor (HGF) (Abstract and columns 7 and 15). Further teaching that the medium for isolation, proliferation and differentiation of the stem cells may be supplemented with a variety of growth factors, that include hepatocytes growth factor (HGF) (column 7). Csete et al. teach that the medium for proliferating the stem cells and the medium for differentiation of these cells can be the same or different (lines 42-45; column 7). Therefore, to the extent that Csete et al. teach growth medium supplemented with HGF and FGF-2 for proliferation and differentiation of the stem cells, they anticipate the instant claims.

Applicants argue that Csete has provided specific information to the skilled person in column 15 for selecting from their long list of potential medium supplements in column 7 for isolating, culturing, proliferating and differentiating neural stem cells in particular, and they do not teach or suggest the claimed methods, i.e., combining HGF with FGF-2. Such is not found persuasive, because Applicants' arguments are based on selective reading of the teachings of Csete et al. and as already indicated, Csete et al. teach that the medium for proliferating the stem

cells and the medium for differentiation of these cells can be the same; and such cannot simply be ignored, because additional embodiments are also taught.

Applicants argue that the passage at column 7, lines 42-62 of Csete is not enabling to those of skill regarding how to proliferate, culture or differentiate any kind of stem cell, much less neural stem cells, because the passage at column 7, lines 42-62 of Csete discloses a list of at least 18 potential medium supplements and does not teach or suggest which supplements to choose for which particular stem cell types (e.g., skeletal muscle, neural, skin, embryonic, etc), or whether the listed variety of medium supplements can be combined or how they would be combined. Further, arguing that if one of skill were to select two of the 18 listed medium supplements and combine them, there would be $17+16+15+14+13+12+11+10+9+8+7+6+5+4+3+2+1=153$ different combinations; that Csete does provide guidance particular to culturing, proliferating and differentiating neural stem cells in column 15, and this disclosure does not teach or suggest the claimed methods.

Such is not found persuasive, because the reference of Csete et al. is a U.S. patent, and as stated in MPEP 716.07, every patent is presumed valid (35 U.S.C. 282), and that presumption includes the presumption of operability (*Metropolitan Eng. Co. v. Coe*, 78 F.2d 199, 25 USPQ 216 (D.C. Cir. 1935). Affidavits or declarations attacking the operability of a patent cited as a reference must rebut the presumption of operability by a preponderance of the evidence. *In re Sasse*, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). Applicants have not provided such affidavit or declaration. Csete et al. specifically describe undifferentiated neural progenitor and stem cells and their isolation, culture and differentiation in medium containing bFGF (column 15, lines 45-60). In addition to bFGF, Csete et al. specifically disclose HGF and six growth factors as suitable supplemental growth factors in medium containing serum (column 7). The disclosure of additional media supplements that are not growth factors is irrelevant, because the issue is whether the combination of HGF and FGF-2 are taught by Csete et al. Supplements such as cytokines cannot necessarily be considered functionally equivalent to growth factors. Moreover, the fact that Csete et al. teach the proliferation and differentiation medium may be supplemented with various growth factors and combinations of growth factors, does not require that every permutation of such factors be utilized. A person of skill having been apprised of the teachings

of proliferating and differentiating neural stem cells in growth medium supplemented with b-FGF, would be taught that the medium may be additionally supplemented with b-FGF and HGF, as taught in column 7. Applicants have further failed to indicate what is considered non-enabling with regard to supplementing culture medium with various combinations of growth factors.

Therefore the rejection of claims is maintained, for reasons of record and the foregoing discussion.

Response & Maintained Claim Rejections - 35 USC § 103

Claims 4-7 and 19-23 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Csete et al. (U.S. Patent No.: 6,589,728; filed Jan. 31, 2001), in view of Luskin (U.S. Patent No.: 5,753,505; filed Jul. 6, 1995). Applicants' cancellation of claims 19-23 renders their rejection moot. The rejection set for the on pp. 4-5 of the office action dated August 3, 2007, and pp. 7-12 of the previous office action dated March 21, 2008 is maintained for reasons of record.

Applicants disagree with the rejection, arguing that no *prima facie* case of obviousness has been established, because Csete does not teach or suggest any method of culturing, proliferating or differentiating a neural stem cell by supplementing a growth medium with a combination of growth factors consisting of HGF and FGF-2, and Luskin does not supply the elements missing from Csete, and the combined disclosures of Csete and Luskin do not teach or suggest any method of culturing, proliferating or differentiating a neural stem cell by supplementing a growth medium with a combination of growth factors *consisting of* HGF and FGF-2. Applicants' arguments have been fully considered but are not found persuasive.

Applicants are referred to the response provided above, regarding the recitation of "consisting of" in the context of the instantly amended claims.

Applicants argue that although Csete expressly and particularly teaches in column 15 that neural stem cells are proliferated in medium containing bFGF or NGF, and differentiated in medium without bFGF, and the Examiner in direct contradiction states that the same proliferating medium containing FGF-2 may thus be used for differentiation. Applicants' argument is not found persuasive, because as already indicated, while Csete's teachings in

column 15, refer the method of Hazel and Muller wherein bFGF is removed from the media in the differentiation step, there is no teaching that the media contains NGF. The only reference to NGF is that it promotes growth of neural cells during development. Further, Csete et al. specifically teach that the medium for proliferation and the medium for differentiation may be the same or different, and can be supplemented with bFGF and HGF. The teachings of column 7 in Csete et al. are applicable to any stem cell and thus Applicants cannot dismiss such teachings, based on the fact that they are not exclusive to neural stem cells.

Applicants argue that the facts of the present case are analogous to those presented in *In re Brian W. Baird*, 16 F.3d 380; 29 USPQ2d 1550 (Fed. Cir. 1994), wherein the claims at issue were directed to a toner comprising a bisphenol A polyester, and that the reference taught away the species of bisphenol A. Further arguing that the teachings in column 7 of Csete et al. does not suggest any correlation between any stem cell type and a medium supplement useful for culturing, proliferation or differentiation. Such is not found persuasive, because the cited case is not on point, and is completely unrelated to the instant invention. Further, there is no teaching away in Csete et al. regarding the inclusion of both bFGF and HGF in the proliferation and differentiation medium, as both are expressly taught in column 7 for proliferation and differentiation of stem cells. Further, there is no requirement that Csete et al. include all their teachings in a contiguous single column of their disclosure. The teachings of column 7 are clearly supplemental to the specific examples taught by the reference.

Applicants argue that any *prima facie* case of obviousness has been rebutted by a showing of synergistic (i.e., more than additive) effects of HGF and FGF-2, because the combination of EGF and FGF-2 had increased effects on proliferation and growth neural stem cells that were clearly not synergistic and less than additive than either EGF or FGF-2 individually, citing Table 1 on page 35 of the Specification; further arguing that the primary reference, Csete, teaches away from the present methods. Regarding the alleged teaching away by Csete et al., Applicants are referred to the response provided above.

Applicants' arguments are not found persuasive, because the instant claims are directed to methods using HGF, and FGF-2, thus effects of EGF are not germane to the instant claims. Further, Table 1 is silent on the concentration of FGF-2 utilized in the experiments, as the only

concentrations provided appear to be for HGF; thus it is unclear what concentration of FGF-2 was included in the assay. Moreover, any "unexpected" results would be so considered in view of an expected result. In the instant case, increased proliferative potential when more than one growth factor is utilized in a culture medium would not be unexpected. As indicated in MPEP 716.02(c), "Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." *In re Gershon*, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967). Additionally, when total cell numbers are computed for HGF (900 +/- 20), and FGF-2 (1750 +/- 55), the expected additive number may well be over 2700, that is close to the combination of HGF and FGF-2 (i.e. 3100 +/- 66). Regardless, no definitive conclusion may be drawn from Table 1, as the table lacks any stated concentration for FGF-2.

Applicants state that the Examiner appears to be basing the present rejections based on the inherent disclosure of Csete, and citing *In re Rijckaert*, argue that any rejection predicated upon "inherent obviousness" is simply in error; further arguing that the list of medium supplements disclosed in column 7, lines 42-62 of Csete, including growth factors, cytokines and hormones of Csete does not teach or suggest combining any supplements, much less particularly two or more growth factors.

In response, it should be noted that the inherency cited in the previous office action was in reference to the number of neurons versus glia cells (limitation of claim 18), and not with reference to the growth factors in column 7 of Csete et al. Claim 18 is not a part of the obviousness rejection, and thus Applicants' arguments are not on point. Moreover, Csete et al.'s teachings with respect to the growth factors in column 7 have already been addressed (*supra*).

Applicants, citing *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, argue that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species.). Here, the long list of medium supplements listed in column 7 of Csete do not in any way call out the selection of the combination of HGF and FGF-2 (or any other combination of medium supplements) for the culturing, proliferation or differentiation of neural stem cells.

Such is not found persuasive, because the issue is the teaching of the combination of HGF and FGF-2 by Csete et al. The inclusion of other supplements are not germane, because such is not a limitation of the instant claims. As such, Csete et al. only disclose six growth factors that may be used in the proliferation and differentiation medium, and additional supplements cannot be considered functional equivalents. As the species of bFGF and HGF are specifically disclosed in the listing, the case law cited by Applicants fails to apply. Further, Csete et al. describe that the medium for proliferating the stem cells and the medium for differentiation of these cells can be the same (lines 42-45; column 7). Accordingly, the same combination of FGF-2 and HGF used in the proliferating medium may thus be used in the differentiation medium. Applicants' argument that HGF is not included in the medium of column 15, and FGF-2 is removed, has been addressed (*supra*).

Therefore the rejection is maintained for reasons of record and the foregoing discussion.

Conclusion

Claims 4-8 and 15-18 are not allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. The claims are drawn to the same invention claimed earlier in the application and would have been finally rejected on the grounds and art of record in the next Office Action if they had been entered earlier in the application. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR § 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Examiner, Art Unit 1633